AMENDMENTS TO THE SPECIFICATION

Please replace all paragraphs found on Page 10 with the following rewritten paragraphs:

Figure 1 depicts a nucleic acid sequence (SEQ ID NO:1) encoding human glial cell line-derived neurotrophic factor receptor ~~(GDNFR-α)~~ (GDNFR-α; SEQ ID NO:2). The amino acid sequence of the full length GDNFR protein is encoded by nucleic acids 540 to 1934 of SEQ ID NO:1.

Figure 2 depicts the amino acid sequence (SEQ ID NO:2) of the full length human GDNFR-α protein.

Figure 3 depicts a nucleic acid sequence (SEQ ID NO:3) encoding rat GDNFR-α (SEQ ID NO:4). The amino acid sequence of the full length GDNFR-α protein is encoded by nucleic acids 302 to 1705 of SEQ ID NO:3.

Figure 4 depicts the amino acid sequence (SEQ ID NO:4) of the full length rat GDNFR-α protein

Figure 5 (A) – (K) depicts the alignment and comparison of portions of GDNFR-α cDNA sequences (SEQ ID NOS:46-55) produced in various clones as well as the consensus sequence for human GDNFR-α (SEQ ID NO:45).

Figure 6 depicts the identification of Neuro-2A derived cell lines expressing GDNFR-α.

Figure 7A and 7B depict the results of the equilibrium binding of [^{125}I]GDNF to cells expressing GDNFR-α.

Please replace the paragraphs beginning on page 11, lines 33, and ending on page 12 line 1, with the following rewritten paragraphs:

Figure 18 depicts the alignment and comparison of various human, rat and mouse GDNFR amino acid sequences (SEQ ID NOS:2, 4, and 56, respectively).

Figure 19 depicts the alignment and comparison of human GDNFR-α, rat, ~~and mouse~~ GDNFR-α, human GRR2, rat GRR2 ~~AND~~ human GRR3 and rat GRR3 amino acid sequences ((SEQ ID NOS:2, 4, 36, 40, 38, and 42, respectively) and an exemplary consensus GDNFR sequence (SEQ ID NO:43).

Please replace the paragraph beginning on page 12, line 3, with the following paragraph:

Figure 20 depicts the alignment and comparison of human GDNFR-α (SEQ ID NO:2)~~and~~ , rat GDNFR-α (SEQ ID NO:4), human GRR2 (SEQ ID NO:36) and rat GRR2 peptide sequences (SEQ ID NO:40).

Please replace the paragraph beginning on page 12, line 24, with the following rewritten paragraph:

Figure 26 depicts the amino acid sequences of rat GDNFR-α, rat GRR2 and rat GRR3 (SEQ ID NOS:4, 40, and 42, respectively) are aligned and a consensus sequence (SEQ ID NO:44) is shown above the three receptor sequences. Upper case letters in the consensus sequence indicate amino acids that are conserved in all three receptors, lower case letters indicate that two of the three receptors share that amino acid, and dots indicate all three receptors have a different amino acid at that position. Predicted signal peptide sequences are underlined in GDNFR-α and GRR3; no signal peptide is predicted for GRR2. The hydrophobic C-terminal regions of all three putative receptors are underlined. Potential N-glycosylation sites are shown in boldface and sites conserved between two receptors are outlined by boxes.

Please replace the paragraph beginning on page 59, line 10, with the following rewritten paragraph:

Immunocytochemical identification of photoreceptors

Photoreceptors were identified by immunostaining for arrestin, a rod-specific antigen. Cultures of photoreceptors were fixed for 30 minutes at room temperature with 4% paraformaldehyde in PBS, pH 7.4, followed by three washes in PBS. The fixed cultures were then incubated in Superblock blocking buffer (Pierce, Rockford, IL) , containing 1% Nonidet P-40 to increase the penetration of the antibodies. The anti-arrestin antibodies (polyclonal rabbit antibody against the synthetic peptide sequence of arrestin: Val-Phe-Glu-Glu-Phe-Ala-Arg-Gln-Asn-Leu-Lys-Cys (SEQ ID NO:57)) were then applied at a dilution of between 1:2000 in the same buffer, and the cultures were incubated for one hour at 37°C on a rotary shaker. After three washes with PBS, the cultures were incubated for one hour at 37°C with goat-anti-rabbit IgG (Vectastain kit from Vector Laboratories, Burlingame, CA) at a 1:500 dilution. After three washes with PBS, the secondary antibodies were then labeled with an avidin-biotin-peroxidase complex diluted at 1:500 (45 minutes at 37°C). After three more washes with PBS, the labeled cell cultures were reacted for 5-20 minutes in a solution of 0.1 M Tris-HCl, pH 7.4, containing 0.04% 3',3'-diaminobenzidine-(HCl)4, 0.06 percent $NiCl_2$ and 0.02 percent hydrogen peroxide. Based on arrestin-immunoreactivity, about 90% of the cells in the cultures were rod photoreceptors.

Please replace the paragraph beginning on page 68, line 21, with the following rewritten paragraph:

Soluble human GDNFR protein products were made. The following examples provide four different forms, differing only at the carboxy terminus, indicated by residue numbering as provided in Figure 2. Two are soluble forms truncated at different points just upstream from the hydrophobic tail and downstream from the last cysteine residue. The other two are the same truncations but with the addition of the "FLAG" sequence, an octapeptide to which a commercial antibody is available (Eastman Kodak). The FLAG sequence is H_2N- DYKDDDDK - COOH (SEQ ID NO:58).

Please replace the paragraph beginning on page 68, line 30, with the following rewritten paragraph:

Lambda phage clone #21, containing nearly the entire coding region of human GDNFR-α, was digested with EcoRI to excise the cDNA insert. This fragment was purified and ligated into EcoRI cut pBKRSV vector (Stratagene, La Jolla, CA) to produce the clone 21-B-3/pBKRSV. Primers 1 and 2 as shown below were used in a PCR reaction with the human GDNFR-α clone 21-B-3/pBKRSV as template. PCR conditions were 94°C, five minutes followed by 25 cycles of 94°C, one minute; 55°C, one minute; 72°C, two minutes and a final extension of five minutes at 72°C. This produced a fragment consisting of nucleotides 1265-1868 of the human GDNFR-α clone plus a termination codon and Hind III restriction site provided by primer 2. This fragment was digested with restriction enzymes Hind III (contained in primer 2) and BglII (position 1304 in human GDNFR-α), and the resulting 572 nucleotide fragment was isolated by gel electrophoresis. This fragment contained the hGDNFR-α- coding region from isoleucine-255 to glycine-443. A similar strategy was used with primers 1 and 3 to produce a fragment with BglII and HindIII ends which coded for isoleucine-255 to proline-446. Primers 4 and 5 were designed to produce fragments coding for the same regions of hGDNFR-α and primers 1 and 3, but with the addition of the Flag peptide coding sequence (IBI/Kodak, New Haven, CN). The Flag peptide sequence consists of eight amino acids (H2N-Asp-Tyr-Lys-Asp-Asp-Asp-Asp-Lys-COOH (SEQ ID NO:61)) to which antibodies are commercially available. Primers 1 and 4 or 1 and 5 were used in PCR reactions with the same template as before, and digested with HindIII and BglII as before. This procedure produced fragments coding for isoleucine-255 to glycine-443 and isoleucine-255 to proline-446, but with the addition of the Flag peptide at their carboxy termini.

Please replace the paragraph beginning on page 87, line 34, with the following rewritten paragraph:

This example describes the cloning of a novel GDNFR-α related receptor, GRR2 (SEQ ID NO:36), and provides evidence that GRR2 is a receptor for neurturin. Analogous to GDNF and GDNFR-α, neurturin effectively binds GRR2 and induces Ret activation. The data also

show that both GDNF and neurturin can interact with either GDNFR-α or GRR2 and activate the Ret PTK in the presence of either binding receptor.

Please replace the paragraph beginning on page 88, line 18, with the following rewritten paragraph:

The amino acid sequences of human GDNFR-α (SEQ ID NO:2), ~~and~~ rat GDNFR-α (SEQ ID NO:4), human GRR2 (SEQ ID NO:36) and rat GRR2 (SEQ ID NO:40)~~and GRR2~~ are aligned. Shaded areas indicate amino acids that are identical in all four sequences. Boxes indicate conservation between rat and human orthologs of the same receptor, but not between GDNFR-α and GRR2.

Please replace the paragraph beginning on page 92, line 27, with the following rewritten paragraph:

A search of the GenBank database for sequences related to GDNFR-α resulted in the identification of EST, H12981.Gb_Est1. Primers corresponding to nucleotides 47 to 65 (5'-CTGCAAGAAGCTGCGCTCC-3') and 244 to 265 (5'-CTTGTCCTCATAGGAGCAGC-3') of H12981.Gb_Est1 (SEQ ID NOS: 59 and 60, respectively) were synthesized and used for RT-PCR with human fetal brain mRNA (Clontech, Cat. #64019-1) as the template. A 218 nt fragment was amplified, subcloned into pBlue-Script (Stratagene, La Jolla, CA), and sequenced to verify its correspondence with the original EST. The fragment was then radiolabeled with [^{32}P]-dCTP using a Random Primed DNA Labeling Kit (Stratagene, La Jolla, CA) according to the manufacturer's instructions. The radio-labeled probe was used to screen a human fetal brain cDNA library (Stratagene, La Jolla, CA). Two million clones were plated on 15 cm agarose plates and replicated on duplicate nitrocellulose filters. The filters were prehybridized at 55°C for 3.5 hours in 200 ml of 6 x SSC, 1 x Denhardts, 0.5% SDS, and 50 μg/ml salmon sperm DNA. Following the addition of 2 x 10^8 cpm of the radiolabeled probe, hybridization was continued for 18 hours. Filters were then washed twice for 30 minutes each at 55°C in 0.2 x SSC, 0.1% SDS and exposed to X-ray film overnight with an intensifying screen. Five positive clones were identified and their DNA sequences were determined.

Please replace the paragraph beginning on page 98, line 17, with the following rewritten paragraph:

An alignment of the amino acid sequences of rat GDNFR-α, rat GRR2, and rat GRR3 (SEQ ID NOS:4, 40, and 42, respectively) is shown in Figure 26. The overall amino acid sequence identity among the three receptors is in the range of 30%-50%. GDNFR-α and GRR2 are somewhat more closely related to each other (48% identity) than they are to GRR3 (35% and 33% identity, respectively). Hydrophobic regions are found at both the amino and carboxy termini of all three molecules, except for the amino terminus of GRR2 (underlined, Figure 26).

The amino terminal regions of both GDNFR-α and GRR3 have the characteristics expected for signal peptide sequences. Although the GRR2 N-terminal sequence does not fit the criteria for a classical signal peptide, there is evidence that GRR2 is secreted. The carboxy terminal hydrophobic region of GDNFR-α is known to be involved in GPI-linkage to the cell membrane, and it is likely that the corresponding regions in GRR2 and GRR3 serve the same purpose. The most striking feature of the sequence alignment is the conservation of 28 cysteine residues among all three receptors (highlighted, Figure 26), indicating that these proteins probably have similar three-dimensional structures. Several potential N-glycosylation sites are present in the receptors (shown in boldface, Figure 26), but none are found at the same position in all three receptors. GDNFR-α and GRR2 share sites at positions 365 and 427 that are not found in GRR3, and GRR2 shares a possible site with GRR3 at positions 322-323 (Figure 26).

Please replace the paragraph beginning on page 98, line 17, with the following rewritten paragraph:

An alignment of the amino acid sequences of rat GDNFR-α, rat GRR2, and rat GRR3 (SEQ ID NOS:4, 40, and 42, respectively) is shown in Figure 26 ~~(SEQ ID NO:44)~~. The overall amino acid sequence identity among the three receptors is in the range of 30%-50%. rat GDNFR-α and rat GRR2 (SEQ ID NOS:4 and 40, respectively) are somewhat more closely related to each other (48% identity) than they are to rat GRR3 (SEQ ID NO:42; ~~(~~35% and 33% identity, respectively). Hydrophobic regions are found at both the amino and carboxy termini of all three molecules, except for the amino terminus of GRR2 (underlined, Figure 26). The amino terminal regions of both rat GDNFR-α and rat GRR3 have the characteristics expected for signal peptide sequences. Although the rat GRR2 N-terminal sequence does not fit the criteria for a classical signal peptide, there is evidence that GRR2 is secreted. The carboxy terminal hydrophobic region of rat GDNFR-α is known to be involved in GPI-linkage to the cell membrane, and it is likely that the corresponding regions in rat GRR2 and rat GRR3 serve the same purpose. The most striking feature of the sequence alignment is the conservation of 28 cysteine residues among all three receptors (highlighted, Figure 26), indicating that these proteins probably have similar three-dimensional structures. Several potential N-glycosylation sites are present in the receptors (shown in boldface, Figure 26), but none are found at the same position in all three receptors. Rat GDNFR-α and rat GRR2 (SEQ ID NOS:4 and 40, respectively) share sites at positions 365 and 427 that are not found in rat GRR3 (SEQ ID NO:42), and rat GRR2 (SEQ ID NO:40) shares a possible site with rat GRR3 (SEQ ID NO:42) at positions 322-323 (Figure 26).

Please replace the paragraph beginning on page 103, line 26, with the following rewritten paragraph:

In situ hybridization using anti-sense riboprobes of GDNF, *ret*, GDNFR-α, GRR2, and GRR3, was done according to Zhou et al. (Journal ~~Of~~ of Neuroscience Research, 37, 129-143, 1994). The *ret* probe is a 316 nt fragment derived from the extracellular domain of the rat *ret* cDNA. GDNF mRNA was detected using a 303 nt fragment of a rat GDNF cDNA clone

(nucleotide #50 to 352, Lin et al., 1993). GDNFR-α transcripts were detected with a 396 nt riboprobe (nucleotides 1072 to 1468). GRR2 transcripts were detected with a 205 nt antisense riboprobe corresponding to amino acids 339-413 of SEQ ID NO:40~~(Figure 26)~~. GRR3 transcripts were detected with a 225 nt antisense riboprobe corresponding to amino acids 239-315 of SEQ ID NO:42~~(Figure 26).~~

Please add the following new paragraph after the paragraph ending on line 1 of page 1.

This application is a continuation-in-part of U.S. patent application Ser. No. 08/837,199, April, 14, 1997, now abandoned, which claims the benefit of U.S. provisional patent applications Ser. Nos. 60/017,221 filed May 9, 1996 and 60/015,907 filed April 22, 1996, which are, in their entirety, hereby incorporated by reference herein.